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FUNCTIONAL INTERACTIONS BETWEEN PI3-KINASE AND NF- κ B SIGNALING PATHWAYS PROMOTE JOINT DESTRUCTION IN RHEUMATOID ARTHRITIS

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Background and objectives Rheumatoid arthritis (RA) synovium is characterised by hyperplasia of fibroblast-like synoviocytes (FLS), which display properties of transformed cells. Regulation of proto-oncogenic phosphatidylinositol 3-kinase (PI3-K) signaling by components of the NF- κ B signal transduction pathway has emerged as a candidate molecular mechanism linking inflammation to cancer. Conversely, activation of PI3-K pathways in genetically engineered mice, via reducing expression of PTEN or FoxO transcription factors or transgenically expressing constitutively active PKB, can drive NF- κ B-mediated autoimmunity. Here we examined potential functional relationships between PI3-K and NF- κ B signaling in RA FLS and synovial tissue.

Materials and methods Expression and/or phosphorylation of IKK β , I κ B α , PTEN, a negative regulator of PI3-kinase, PKB and FoxO1, downstream targets of PI3-kinase, was detected by immunohistochemistry combined with digital image analysis in synovial tissue from 15 disease-modifying anti-rheumatic drug (DMARD)-naïve RA patients. Biopsies were obtained at baseline, and x-rays made of hands and feet at baseline and at 2 years follow-up. At 2 years, patients were classified as having non-erosive or erosive disease (Sharp van der Heijde score > 2). Effects of the pan-PI3-K inhibitor LY294002 and inhibitors specific for α/β , γ and δ isoforms of PI3-K on RA FLS IL-1 β -induced I κ B α phosphorylation and NF- κ B p65 activation were assessed by immunoblotting and ELISA, respectively.

Results In vivo we observed a strong correlation between expression of IKK β and phosphorylation of I κ B α ($r = 0.83$, p

< 0.005) in RA synovial tissue, but IKK β did not downregulate PTEN or FoxO protein expression, as predicted by tumour models. Instead, we observed a strong positive correlation between PKB activation, phosphorylation of FoxO1 ($r = 0.90$, $p < 0.0001$) and activation of NF- κ B signalling ($r = 0.56$, $p < 0.05$), and NF- κ B signaling was elevated in patients with accelerated progressive disease ($p < 0.05$). In vitro, sustained phosphorylation of I κ B α and activation of NF- κ B in RA FLS by IL-1 β stimulation required PI3-K activity.

Conclusions Our studies provide evidence that PI3-K signaling pathways may contribute to joint destruction in RA through enhancement of NF- κ B-dependent gene transcription and that PI3-kinase inhibitors may be effective in preventing disease progression.